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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/966,768	09/28/2001	Derek Van Der Kooy	Bereskin & Parr	6817

110 7590 11/20/2003

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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 11/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/966,768	VAN DER KOOY ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 6 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-17,20-22,25-38,40-43 and 47-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-11,13-17,20-22,25-27,29-32,37,38 and 47-49* is/are allowed.

6)☒ Claim(s) *28,33-36 and 40-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Non-Final Office Action is a response to the Amendment under 37 CFR §1.111 filed 27 August 2003 (hereinafter, 27 August Amendment) and Declaration under 37 CFR 1.132 filed 27 August 2003 in reply to the Non-Final Office Action mailed 23 May 2003 (hereinafter, 23 May Office Action). Claims 1-50 were considered in the 23 May Office Action. Claims 12, 18, 19, 23, 24, 39 and 44-46 were canceled and claims 1, 20, 28, 29, 31, 33, 35, 37, 43 and 47 were amended in the 27 August Amendment. Claims 1-11, 13-17, 20-22, 25-38, 40-43 and 47-49 are pending and under consideration.

Response to Amendment

Rejection of claims 12, 18, 19, 23, 24, 39, 44-46 and 50 is rendered moot by cancellation of the claims.

Claim Rejections - 35 USC § 112, first paragraph

Rejection of claim 17 under 35 U.S.C. 112, first paragraph, as lacking adequate written is withdrawn.

Rejection of claims 1, 2, 3-11, 14-17, 20-22, 28, 31-38, 40-43 and 47 under 35 U.S.C. 112, first paragraph as lacking enablement for the full scope of the claimed subject matter is withdrawn.

Claim Rejections - 35 USC § 102

Rejection of claims 33-40 under 35 U.S.C. 102(a) as anticipated by Tropepe *et al.* (1999) *Soc. Neurosci. Abstracts* 25: 527 is withdrawn in view of the Declaration.

New Grounds

Claim Objections

Claim 28 is objected to because of the following informalities: There is a typographical error in the first line (i.e., "according to of claim"). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35 and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for screening for differentiation factors of cellular development comprising culturing pluripotent embryonic stem cells at low cell density, does not reasonably provide enablement for the method comprising culturing cells other than pluripotent stem cells at low cell density. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claims are directed to a method of screening for differentiation factors, which comprises the method step of culturing "the cells" at low cell density in serum free media. The specification states, "low cell density as used herein refers to a cell culture density at which cell proliferation can occur with minimal and preferably no aggregation of ES cells or EB formation" (page 14, lines 17-19). Thus, the claim appears to encompass a method of culturing any cell at a density at which cell proliferation can occur with minimal and preferably no aggregation of ES cells or EB formation. As discussed below, it is unclear what exactly is meant by culturing a cell that is not an ES cell at a density wherein there is no aggregation of ES cells or EB formation. However, even if the limitation of "low cell density" is afforded a more definite meaning such as "50 or fewer cells/μl" (page 14, line 20), the disclosure fails to enable the full scope of the claimed subject matter because practicing the invention commensurate with the full scope of the claims would require undue experimentation.

Amount of direction provided by the inventor and existence of working examples: Although the claims encompass a method for screening for differentiation factors wherein any

cell is cultured at low density in serum free media, all of the teachings set forth in the specification are directed to methods of culturing and producing pluripotent cells from ES cells. Thus, as the specification fails to teach how the claimed method can be practiced with any cell other than an ES cell, the skilled artisan seeking to practice the full scope of the claimed method must rely on the prior art to teach how to practice the method with cells other than ES cells.

State of the prior art and level of predictability in the art: First, according to sound scientific reasoning, practicing the claimed method of screening for differentiation factors wherein the cells are terminally differentiated or nearly terminally differentiated is highly unpredictable. This is because highly differentiated cells would be expected to change very little during differentiation and the skilled artisan would therefore not know how to detect differentiation of the cells. Furthermore, the art teaches that the culture conditions set forth in the claim would actually prevent differentiation of some cells. Neophytou *et al.* (1997) *Development* 124 :2345-2354 teaches that low cell density and LIF inhibit differentiation of neonatal mouse retinal cells into rod-type photoreceptors (see especially the final sentence in the paragraph bridging the left and right columns on page 2347 and the section entitled "CNTF and LIF arrest rod differentiation" beginning on page 2349). Thus, the skilled artisan cannot readily predict which cells could be used in a method for screening for differentiation factors comprising culturing the cells in serum free media comprising LIF at low cell density.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the presence of inoperative embodiments within the scope of the claim does not necessarily render a claim non-enabled (see *Atlas Powder Co. v. E.I. du Pont de Nemours & Co* (224 USPQ 409, 414; hereinafter *Atlas*). *Atlas* also provides, "[o]f course, if the

number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid" (page 414). In the instant case, the claims are generic to methods of using widely divergent cell types to screen for differentiation factors. However, the art and sound scientific reasoning indicate that many embodiments encompassed by the claims would be inoperative, and the skilled artisan would not be able to predict which of the embodiments that were conceived but not yet made would be operative or inoperative without having to make and test each one. This would clearly require undue experimentation as the specification provides guidance only with respect to ES cells. Therefore, practicing the claimed invention commensurate with its full scope would require undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28, 33-36 and 40-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28, 36 and 40-43 are indefinite in that they recite an intended use for the claimed method that is distinct from the intended use of the methods from which they depend but fail to set forth any method steps that would accomplish the intended use. As such, the terminal process step set forth in the method does not clearly relate back to the preamble. It is therefore unclear whether the use set forth in the preamble requires additional process steps that are not set forth in the body of the claim.

Claim 33 is indefinite because there appears to be a conjunction missing in the fourth line of part "a". It is therefore unclear how the second statement set forth in part "a" is related to the first statement and the remainder of the process steps set forth. Also, it is unclear to which conditions the detection step of part "b" is referring. Is differentiation determined only in the presence of the potential modulator? If so, what is the purpose of the second set of conditions in part "a"? Claim 34 is indefinite insofar as it depends from claim 33.

Claim 35 is indefinite in the recitation of "the cells" in the first line of part "a." There is no antecedent basis for "the cell" in the claim. Furthermore, the claim is indefinite in the limitation "at low cell density". "Low cell density" is defined in the specification as "a cell culture density at which cell proliferation can occur with minimal and preferably no aggregation of ES cells or EB formation". As the majority of cells encompassed by "the cell" of the claims (i.e., those that are not ES cells) would not form embryoid bodies or produce aggregation of ES cells, it is unclear how the limitation to low cell density applies to cell types other than ES cells.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DMS

DAVID GUZO
PRIMARY EXAMINER